BRAIN MRI AND MRS IMAGING FOR DIAGNOSTIC EVALUATION OF BILIRUBIN ENCEPHALOPATHY IN THE NEWBORN

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ABSTRACT

Background & purposes: MR examination of infants with kernicterus shows abnormal changes in signal intensity in various parts of the brain, including the globus pallidus and subthalamic regions. The purpose of this study was to see if the MR spectroscopic profiles of infants with hyperbilirubinemia and symptoms of kernicterus provide new insights into the pathophysiology of bilirubin and early diagnosis of bilirubin encephalopathy.

Methods: This observational comparative study was done at Sayed Galal Univesity Hospital between June 2015 to December 2015. Eighteen newborns, with hyperbilirubinemia were divided into 2 groups; **Group one:** newborns with neonatal Hyperbilinaemia without encephalopathy (12 cases). **Group two**: newborns with neonatal Hyperbilinaemia and encephalopathy (NBE) diagnosed by BIND score (Bilirubin Induced Neurological Dysfunction Score) (6 cases). Brain MRI and MRS were done to both groups and the differences in imaging, clinical and biochemical data between both groups were evaluated statistically. Ethical committee approval and parent consent were obtained before the start of the study.

Results: In our study, one case only in group II had abnormal increased signal intensity in the globus pallidus on T1-weighed MRI. However, we clearly demonstrated abnormal metabolism in MRS study with a decreased NAA/ Cr (N Acetyl Aspartate/ Creatine), and Cho/Cr (Choline/Creatine) ratios in the basal ganglia in the 6 neonates of group II.

Conclusion and Recommendations: MRS is useful in the differential diagnosis of patients with NBE from patients with NH, especially when the symptoms of patients with NBE are subtle and MRI does not reveal clear obvious abnormalities.

Key words: Kernicterus, Newborn, MRS, MRI.

INTRODUCTION

Neonatal bilirubin encephalopathy, also known as neonatal kernicterus, is the most serious complication of neonatal hyperbilirubinemia. Because symptoms are either subtle or absent and patients with the disease may not always exhibit definite neurological signs during the neonatal period, the clinical diagnosis of neonatal bilirubin encephalopathy

is quite difficult (1). Magnetic resonance imaging (MRI) in the diagnosis of neonatal bilirubin encephalopathy is an important auxiliary examination.

MRI during the acute phase of kernicterus has already been described as abnormally increased signal intensity on T1-weighted images in the globus pallidus and subthalamic nuclei. Furthermore, abnormally increased signal intensity on T2-weighted MR images of the globus pallidus and subthalamic nuclei in the subacute and chronic phases of kernicterus were well described (2).

Magnatic Resonance Spectroscopy (MRS) has been applied extensively in clinical research, and is recognized as a valuable tool for noninvasive monitoring of brain biochemistry in vivo for both animals and humans. The metabolites in the central nervous system most amenable for study with 1H-MRS are NAA (N Acetyl Aspartate), Cr (total Creatine), and Cho (Choline). Moreover, the ratio of NAA/Cr is considered to be a metabolic marker of the functional status of neurons and axons in the brain, with a decrease in the ratio indicating neuronal or axonal loss or dysfunction(3).

AIM OF THE STUDY

The purpose of this study was to evaluate the diagnostic value of conventional magnetic resonance imaging (MRI), and proton magnetic resonance spectroscopy (MRS) for diagnosis of neonatal bilirubin encephalopathy.

PATIENTS AND METHODS

This observational comparative study was done on 18 jaundiced newborns selected from NICU of Sayed Galal University Hospital in the period between June 2015 to December 2015, with the following **inclusion criteria;**

1. Full term newborns(>37 weeks or more) .
2. Total serum bilirubin >20 mg/ dl.

Exclusion criteria:

1. Newborns with neurological insults affecting BIND score (HIE, Metabolic errors…etc)
2. Preterm newborns < 37 Weeks.
3. Newborns with direct Hyperbilirubnaimia > 20% of total bilirubin.
4. Newborns with Total bilirubin <20 mg/dl

Then all newborns were divided into 2 groups;

Group I: Babies with neonatal Hyperbilinaemia without encephalopathy (12 cases).

Group II: babies with neonatal Hyperbilinaemia and encephalopathy diagnosed by BIND score (6 cases).

All newborns included in the study were subjected to the following:

I. Thorough history empathizing the onset of jaundice, maternal blood group, maternal medications, sex, Apgar score.

II. Thorough clinical examination including:
- @ Balard score to assess the gestational age
- @ BIND Score.
- @ Anthropometric measures (weight, length & Head C.)
- @ Systemic examination

Parameter	Finding	Points
cry pattern	normal	0
	high-pitched	1
	piercing, shrill, frequency decreased or increased	2
	inconsolable or cries only with stimulation	3
behavior and mental status	normal	0
	sleepy, poor feeding	1
	lethargy, very poor feeding, irritable	2
	semi-coma, intermittent apnea, seizures	3
muscle tone	normal	0
	variable hypotonia	1
	moderate hyper or hypotonia, posturing, bicycling, nuchal or truncal arching	2
	severe hyper or hypotonia, opisthotonus, fever	3

Advanced ABE :(Acute Bilirubin Encephalopathy) (score 7-9).
Moderate ABE :(score 4-6).
Mild ABE :(score 1-3)

III. Laboratory investigations including:

- Complete Blood Picture, total serum bilirubin, , direct serum

bilirubin, Retecleocytic count, coob's test, blood group of the baby and mother,

- Finally Brain MRI and MRS were done to all cases.

IV. MRI and MRS Protocol:

The MRI and MRS examinations were performed in all the patients in one session. They were performed at 1.5 Tesla super conducting system (achieva Phillips MRI machine) manufactured at 2009, Netherlands.

The conventional imaging protocol consisted of a transverse T2 weighted spin echo sequence (TR,4200 ms; TE, 98 ms) and coronal, sagittal, and transverse T1 weighted sequences (TR, 450 ms; TE, 10 ms) with a slice thickness of 4 mm, a matrix of 202×256 pixels, and a field of view of 210×240 mm

Single voxel MRS data was acquired using a point resolved spatially localized spectroscopy pulse sequence with chemical shift –selective water suppression. An automated shimming procedure focused on the water signal was performed to obtain a uniform and homogenous magnetic field. Moreover, both shimming and water suppression routines were performed with automatic adjustments. Baseline correction and curve fitting were performed.

Spectral parameters are as follows:
TE=144ms,TE=35,TR=1500ms,slice thickness =10mm,matrix size =16x6 and field of view =160x160mm ,the spectroscopic region of interest is the basal ganglia , this region was also carefully scanned to avoid interference from the surrendering bone and cerebrospinal fluid. Spatial resolution of the MRS images obtained is 1x1x1cm3

NAA/Cr, Cho/Cr,GLX/Cr, Tau/Cr peak –area ratios for the region of interest were generated by soft ware from Philips ,these ratios were compared with normal reference values.

Ethical Considerations:

No conflict of interest, neither financial nor commercial. There was

Ethical committee approval and parent consent were obtained before the start of the study.

Statistics design

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t- test, paired t-test, Chi-square and Linear Correlation Coefficient by SPSS V17.

Linear Correlation coefficient was used for detection of correla-

tion between two quantitative variables in one group.

RESULTS

Table (2): Clinical data of studied groups.

	Group I 12(100%)	**Group II 6 (100%)**	**P value**
Age on admission(days)	4 (3-7)	4 (4-6)	0.470
Age on imaging(days)	18 (12-20)	20(17-22)	0.037*
BIND score	0 (0-0)	5(1-7)	<0.001*
Onset of jaundice(days)	2.75 (2-3)	2 (2-4)	0.085
Maximum bilirubin(mg/dl) (mean ± SD)	27.78±1.95	36.21±7.96	0.003*
Duration of admission (mean ± SD)	3.77±1.05	7.22±2.17	<0.001*
ABO incompatibility	7 (58.3%)	5 (83.3%)	0.596
Rh incompatibility	5 (41.7%)	1(16.7%)	0.596
Reticulocytic count (%)	7% (1-21)	12% (1-17)	0.888
Positive Coombs test	4(33.3%)	3 (50%)	0.864

Concerning laboratory results, there was a significant difference in the total serum bilirubin peak level and BIND score between patients with NBE and patients of NH group while no significant difference was found in other parameter .

Table (3): BIND score items of studied groups.

	group II 6 (100%)
High pitched cry	6 (100%)
Sleepiness	3 (50%)
Arching neck	3 (50%)
Seizures	1 (16.7%)
Opsithotonus	1 (16.7%)

Signs of encephalopathy: High pitched cry sign was present in all cases (100%), sleepiness and arching neck signs were present in 3 cases (50%) while seizures and opsithotonus signs were present in one case (25%).

Table (4): MRI findings of studied groups:

Groups / Findings	Groups		Chi-Square	
	Group I 12 (100%)	Group II 6 (100%)	X^2	P value
Hyperintensity of globus pallidus (T1 WI)	0 (0.0%)	1 (16.7%)	2.118	0.146

Hyperintensity of globus pallidus is considered as radiological sign of bilirubin encephalopathy, however only one case in the NBE group had abnormal increased signal intensity in the globus pallidus on T1- weighed MRI while no patients in the NH group had abnormal increased signal intensity in the globus pallidus on T1- weighed MRI.

Table (5): Comparison of MRS Metabolic Findings in Studied Groups.

	Groups						T-Test	
	Group I			Group II				
	Mean	±	SD	Mean	±	SD	t	P-value
Tau/Cr	0.282	±	0.064	0.433	±	0.101	-3.894	0.001*
Cho/Cr	1.753	±	0.648	1.050	±	0.412	2.404	0.029*
NAA/Cr	1.281	±	0.292	1.006	±	0.204	2.056	0.056
Glx/Cr	0.732	±	0.420	0.634	±	0.502	0.440	0.666

Taurin ratio increased in group II in comparison group I with significant P value. On the other hand NAA/Cr, Cho/Cr and Glx/Cr ratios all are lower ingroup II in comparison to group I (only significant P value in Cho/Cr ratio).

Normal Reference of metabolic ratios:
Cho/Cr= 1.69, NAA/Cr= 1.83, Glx/cr =1.39 , Tau/Cr = 2.39

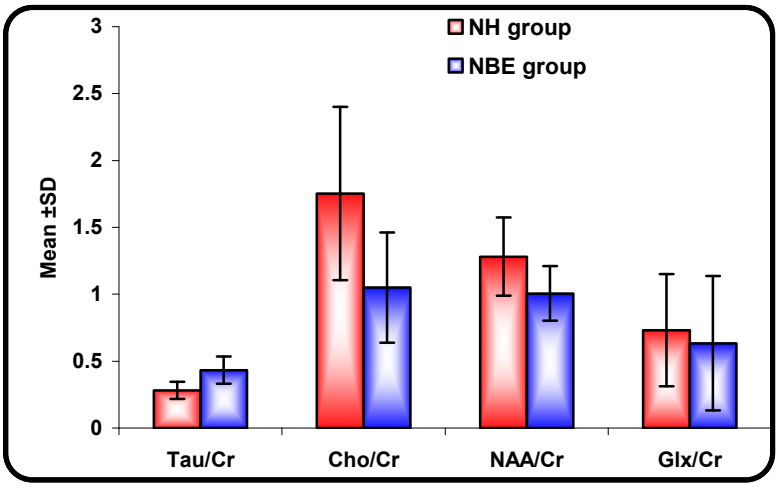
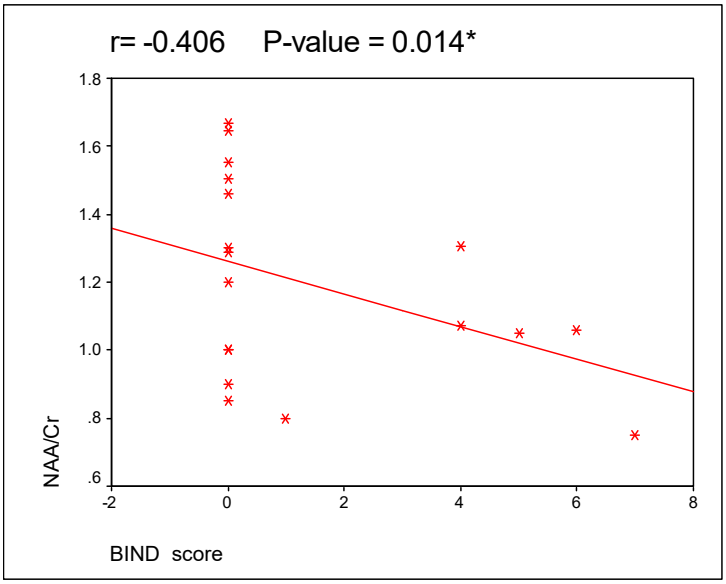


Figure (1): Comparison of MRS Metabolic Findings in Studied Groups.

Table (6): Correlation between metabolites ratios & BIND score.

Correlations		
	BIND score	
	r	**P-value**
NAA/Cr	-0.406	0.014*
Cho/Cr	-0.324	0.003*
Glx/Cr	-0.078	0.757
Tau/Cr	0.697	0.001*

There was a significant negative correlation between NAA/Cr, and Cho/Cr ratios and BIND score. On the other hand there was a positive correlation between Tau/Cr and BIND score.



(Figure 2) Correlation between NAA/Cr & BIND score.

Table (7): Correlation between metabolites ratios & Maximum Bilirubin level.

Correlations		
	Maximum bilirubin	
	r	**P-value**
NAA/Cr	-0.249	0.020*
Cho/Cr	-0.283	0.004*
Glx/Cr	0.100	0.693
Tau/Cr	0.295	0.001*

There was a significant negative correlation between NAA/Cr, and Cho/Cr ratios and maximum bilirubin level. On the other hand there was a positive correlation between Tau/Cr and maximum bilirubin level.

* Significant P value

DISCUSSION

When serum bilirubin exceeds the binding capacity of albumin, or when the blood-brain barrier is immature or injured, bilirubin can enter the brain, especially in premature and low birth weight infants, resulting in encephalopathy called kernicterus(5). Serum bilirubin levels alone are poor predictors of kernicterus especially in sick preterm infants. We need a rapid noninvasive indicator of neurotoxicity and impending cell injury(6).

According to our experience, T2-weighted magnetic resonance images with high signal intensity on the basal ganglia and thalamus in the acute stage of kernicterus is rarely seen(7).

Magnetic resonance spectroscopy (MRS) is a non-invasive method, which can be performed following a routine magnetic resonance investigation within the same examination and can provide very useful molecular information related to the metabolism and function of the normal and pathological structures of the brain (7).

The aim of our study to evaluate the usefulness of MRS in early detection of bilirubin encephalopathy in neonates with hyperbilirubinamia. Also we compare both imaging techniques (MRI & MRS) in diagnosis of kernicterus.

The study was conducted in the neonatal intensive care unit (NICU) sayed galal University Hospital.

The study included 18 patients presenting with peak TSB over 20mg/dl. Twelve cases with neonatal hyperbilirubinaemia without encephalopathy (group I). Six of cases diagnosed NH by BIND score(group II)(table1).

In our study 12 cases presented with ABO incopmitability (12/18), (66%). While, 6 neonates (6/18) (33 %) were Rh incompitability (table 2). **Edris and his college (8)** reported 37% of their patients had ABO incompatibility and 8.8% of patients had Rh incompatibility. This may reflect the extreme importance of antenatal screening of hemolytic disease of the newborn (ABO and Rh incompatability) for prevention of bilirubin encephalopathy. All pregnant women should be tested for ABO and Rh typing.

In the current study BIND score (Bilirubin Induced Neurological Dysfunction) was done to diagnose neonatal hyperbilirubin encephalopathy. The findings of the score are as follow (Table 3):

- High pitched cry in all neonates with encephalopathy (6/6, 100%),
- Sleepiness (3/6, 50%), Arching neck (3/6, 50%), seizures (1/6, 17%), opsithotonus (1/6, 17%).

The presence of any of the above manifestations in a jaundiced neonate is alarming to early intervention and management to control jaundice and prevent its brain complications.

In a study done by **Seoud & her colleagues(9)**, at NICU of children Hospital of Abo El Reash, Cairo university, the common presenting manifestations of newborns with kernicters were as follow:

Poor feeding (95%), irritability (84%), abnormal movements and seizures 50%, opithotonus (33%), hypotonia (28%), and apnea (22%).

They don't use the BIND score in their evaluation.

In our study, one case only in group II had abnormal increased signal intensity in the globus pallidus on T1- weighed MRI. However, by MRS study we clearly demonstrated abnormal metabolism with a decreased NAA/Cr and Cho/Cr ratios in the basal ganglia in the 6 neonates (100%) of NBE group (table4). The present study demonstrated that MRS in NBE can detect brain abnormalities that are not visible on conventional MRI. Although, conventional MRI may not reveal obvious abnormalities in some NBE patients, deposition of bilirubin and neuronal loss in the basal ganglia existed in these patients.

In this study, the ratios of NAA/Cr and Cho/Cr were found to be lower in group II compared with group I and normal reference values. This may be due to neuronal loss in patients with NBE that occurred mainly in the basal ganglia.

In study done by **Wu and his collages (2),** peak area ratios of NAA/Cr in the basal ganglia were found to be significantly lower for the NBE group compared with the NH group and control groups and this is similar with our results. However, in their study there was no significant difference in the NAA/Cr ratios calculated for basal ganglia of the NH and control groups, which is not consistent with our findings.

Also, the peak area ratios of NAA/Cr in the thalamus were decreased for the NBE group compared with the NH and control groups but the differences were

not significant. The estimation of metabolite ratios in the thalamus is short-coming in our spectroscopic study.

Similarly in **Wendy et al 2005 (10),** the ratio of NAA/Cr in the basal ganglia was found to be significantly lower for the NBE group compared with control group. Moreover, **Parashari**'s study (11) revealed significantly elevated Tau/Cr, Glx/Cr and mI/Cr in patients with bilirubin encephalopathy. This is consistent with our results which revealed elevated Tau/Cr and Glx/Cr ratios in NBE group compared with NH group.

Also, our study suggested that there was a negative significant correlation between NAA/Cr and Cho/Cr ratios and maximum bilirubin level. **Wu et al 2013(2)** found that there was a significant correlation between NAA/Cr ratios in the basal ganglia and the total serum bilirubin peak levels in the NBE group. This may be due to neuronal or axonal loss or dysfunction, resulting from preferential deposition of bilirubin in the globus pallidus. However, no correlation was found between NAA/Cr ratios in the basal ganglia and the total serum bilirubin peak levels in the NH group in their study. Further studies will be necessary to clarify this issue.

CONCLUSION AND RECOMMENDATIONS

MRS is useful in the differential diagnosis of patients with NBE from patients with NH, especially when the symptoms of patients with NBE are subtle and MRI does not reveal clear obvious abnormalities.

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دور الرنين المغناطيسي و الرنين المغناطيسي الطيفي في تشخيص الاعتلال الدماغي نتيجة ارتفاع نسبه البلروبين في الأطفال حديثي الولادة

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يعتبر متلازم اعتلال الدماغ نتيجة ارتفاع نسبة البيليروبين اخطر مضاعفات ارتفاع نسبة البيليروبين بالدم فى حديثى الولادة. ونظرا لعدم وجود الاعراض فى كثير من الاطفال المصابين بالمرض, لا يمكن الاعتماد على التشخيص الاكلينيكى. لذلك يعتبر الرنين المغناطيسى عامل مساعد فى التشخيص.

الغرض من الدراسة: تهدف هذه الدراسة لتقييم فائدة الرنين المغناطيسى الطيفى فى التفرقة بين متلازم اعتلال الدماغ نتيجة ارتفاع نسبة البيليروبين و الارتفاع الحاد فى نسبة البيليروبين بالدم فى حديثى الولادة.

طريقة البحث: هذا وقد اشتملت الدراسة على 18 طفل مصابين بارتفاع حاد فى نسبة البيليروبين بالدم بمستشفى باب الشعرية الجامعي. تم تقسيمهم الى مجموعتين: 1- مجموعة مصابة بارتفاع حاد فى نسبة البيليروبين بالدم بدون تأثير علي الدماغ(12 مريض).2- مجموعة مصابة بمتلازم اعتلال الدماغ نتيجة ارتفاع نسبة البيليروبين(6 مرضى).

وقد تم عمل الاتى: تسجيل التاريخ المرضى لكل المرضى, فحص شامل, تحاليل و أشعة الرنين المغناطيسى و الرنين المغناطيسى الطيفى.

نتائج البحث:

بالنظر الى النتائج وجد ان:

- كان هناك فرق كبير فى نسبة البيليروبين بالدم بين المجوعتين.
- لم يكن هناك فرق كبير فى اختبار الكومبزو نسبة الريتكس بين المجوعتين.
- كان هناك فرق كبير فى عند متابعة النمو الحركى و الذهنى بين المجوعتين.
- ظهرت تغيرات الرنين المغناطيسى عند حاله واحده فقط فى المجموعة المصابة بمتلازم اعتلال الدماغ نتيجة ارتفاع نسبة البيليروبين بينما لم تظهر في حالات المجموعة المصابة بارتفاع حاد فى نسبة البيليروبين بالدم.
- كانت نسب أيض الرنين المغناطيسى الطيفى في المجموعة المصابة بمتلازم اعتلال الدماغ نتيجة ارتفاع نسبة البيليروبين (المجموعه 1) أقل من المجموعة المصابة بارتفاع حاد فى نسبة البيليروبين بالدم (المجموعه 2).

التوصيات: بناءا على ما سبق, تثبت هذه الرسالة فائدة الرنين المغناطيسى الطيفى فى التفرقة بين متلازم اعتلال الدماغ نتيجة ارتفاع نسبة البيليروبين و الارتفاع الحاد فى نسبة البيليروبين بالدم فى حديثى الولادة.